THE LONGITUDINAL COURSE OF FATIGUE IN ANCA ASSOCIATED VASCULITIS

Running title ANCA and Fatigue

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Abstract

OBJECTIVE:

Fatigue is common and burdensome in ANCA-associated vasculitis (AAV). This study aimed to understand how fatigue changes over time following treatment initiation and determine whether individuals with the poorest prognosis can be robustly identified.

METHODS:

149 patients with AAV and new onset disease recruited to two clinical trials (RITUXIVAS and MYCYC) were followed for 18 months. Fatigue was measured at baseline and 6 monthly intervals using the vitality domain of the SF-36 quality of life questionnaire and compared to a cohort of 470 controls. Group-based trajectory modelling (GBTM) determined trajectories of the symptom between which baseline characteristics and on-going fatigue scores were compared.

RESULTS:

Fatigue levels at diagnosis were worse in patients than controls (median 30 IQR 10, 48 vs 70 IQR 55, 80; $p<0.001$), with 46% of patients reporting severe fatigue. Fatigue improved after 6 months treatment but remained worse than controls ($p<0.001$). GBTM revealed varied trajectories of fatigue: low fatigue stable (n=23), moderate baseline fatigue improver (n=29), high baseline fatigue improver (n=61) and stable baseline high fatigue (n=37). Participants who followed stable high fatigue trajectories had lower vasculitis activity compared to improvers but no other demographic or clinical variables differed.

CONCLUSION:

This study longitudinally measured fatigue levels in patients with AAV. Although, most patients improve following treatment, an important subgroup of patients report persistent high levels of fatigue that does not change. Few clinical or laboratory markers distinguished these patients, suggesting alternative interventions specific for fatigue are required.

Trial registration

RITUXVAS EudraCT Number: 2005-003610-15 registered 27/9/05

MYCYC EudraCT Number: 2006-001663-33 Registered 21/12/06

Earlier recognition and the successful introduction of immunosuppressive regimens to treat ANCA-associated vasculitis (AAV) have transformed the outcome of these life threatening diseases(1). Mortality rates have been reduced to 20% at 5 years, however relapses and chronic damage are now dominate patient outcomes (2). Reduced quality of life remains common despite disease remission and successful control of the inflammatory process (3). Previous studies have identified fatigue as the most significant determinant of poor quality of life for patients with AAV with more than 90% of patients reporting fatigue to be the most important limiting factor (4-6). Fatigue in AAV has also been linked to reduced social participation, social withdrawal and unemployment (7, 8). However, little is known about the longitudinal nature of this important symptom as all previously published studies investigating patients with AAV and fatigue have been cross-sectional in nature.

Our previous cross-sectional studies in AAV have suggested fatigue is multi-factorial in origin (9, 10). Sleep disturbance, pain and inflammation, as measured by C reactive protein (CRP), were all associated with fatigue, although the association with inflammation was the weakest(10). In a further study of AAV patients in remission, fatigue was associated with heightened perception of exertion, depression, anxiety, and sleep disturbance suggesting that fatigue is of a central origin rather than originating due to problems with muscle or the cardiovascular system (9). Considering the multifactorial nature of fatigue it seems unlikely that the change over time of this complex symptom will be homogeneous; examining average change over time may hide variability in fatigue response to treatment. No previous studies have investigated change in fatigue longitudinally in AAV patients. This is supported by recent findings in patients with rheumatoid arthritis (RA) that suggest the experience of fatigue over time is not uniform; there are subgroups of patients in whom it improves while for others it remains a persistent problem despite treatment (11, 12). It is unknown whether this is also true for patients with AAV.

The aim of this study was to describe the longitudinal experience of fatigue, following treatment initiation, in an inception cohort of patients with generalized AAV recruited to two clinical trials. It

sought to determine how fatigue responds to treatment at a group level, and whether important subgroups of patients could be identified, between whom fatigue response differs. Finally it aimed to characterise those who experienced the poorest fatigue prognosis.

Methods

Patient population

Newly diagnosed patients with generalised AAV recruited to two European Vasculitis Study Group (EUVAS) clinical trials (RITUXVAS and MYCYC) between 2006 and 2011 were included in this study. Briefly, RITUXVAS compared rituximab plus 2 doses of cyclophosphamide for inducing remission with conventionally dosed pulse cyclophosphamide followed by azathioprine for maintenance therapy(13). MYCYC compared mycophenolate mofetil with pulsed cyclophosphamide for 3-6 months until remission and then transferred to azathioprine for maintenance therapy(14). All patients received prednisolone, initially 1mg/kg body weight per day tapered to 12.5 mg per day at the end of month three and to 5mg per day by 18 months.

For this study, patients who had completed at least two SF-36 health related quality of life questionnaires, including baseline were included; 33 RITUXVAS patients, 117 MYCYC patients.

General population controls were identified from a UK commercial online sampling frame (www.192.com), a representative source shown to have >80% population coverage(15),and mailed an SF36 questionnaire. The sample was originally selected to be age and gender matched to a large UK AAV cohort(6).

Data collection

MYCYC followed patients for 18 months while RITUXVAS followed patients for 24 months. For consistency, we used the 18 month time point as the end date for this study. The following data were collected at six-monthly intervals during the trials and used in this study; age, sex, clinical diagnosis (granulomatosis with polyangiitis vs microscopic polyangiitis), ANCA serology, disease activity measured using the Birmingham Vasculitis Activity Score 2003 (BVASv3), assessment of damage using the Vasculitis Damage Index (VDI), dialysis dependency and time to clinical remission (as defined in the original trial protocols, as the complete absence of clinical disease activity using the BVAS item list on two separate occasions and supported by a normal CRP concentration); laboratory data including serum creatinine concentration; CRP; treatment, defined by the induction regime (pulse cyclophosphamide, mycophenolate or rituximab), and the 36 item health related quality of life questionnaire Short Form Health Survey (SF-36).

The primary outcome for this study was change in fatigue as defined using the vitality domain of the SF-36. SF-36 contains 36 items that assess health related quality of life in eight health dimensions: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The SF-36 has performed well in previous AAV studies(16) and has been endorsed as a core AAV outcome measure by Outcome Measures in Rheumatology (OMERACT)(17). SF-36 fatigue domain scores 4 items and is negatively scored with a range 0-100 so that lower scores indicate more fatigue. It has been shown to be a valid measure of fatigue(18, 19).

Ethics

The study was conducted in compliance with the Helsinki Declaration. The two trials were sponsored by Cambridge University Hospitals NHS Foundation Trust. Vifor Pharma (previously Aspreva Pharmaceuticals) provided a research grant to cover the trial and MMF costs for MYCYC and F. Hoffmann–La Roche provided the rituximab and a research grant that contributed to trial costs for RITUXIVAS. The trials received ethical approval from for MYCYC and ethics committee of each

participating center and were conducted according to the European Union Clinical Trials Directive (Directive 2001 EU/20/EC), (EudraCT numbers, 2006-001663-33 and 2005-003610-15 the Oxfordshire Research Ethics Committee B (reference number 06/Q1605/120)). Regulatory approval was obtained from the national regulatory authorities in each country. Written informed consent was obtained from each participant. The control data collection study was approved for conduct by the University of Aberdeen College of Life Sciences Ethics Review Board (ref: CERB/2010/1/493).

Statistics

Quantitative data is described as mean and standard deviation for normally distributed variables and median with interquartile range (IQR) for non-normally distributed variables.

Differences in quantitative data were tested with student's t test (with Welch's correction for unequal variances if appropriate) or the Mann Whitney U test depending on data distribution. Differences in fatigue scores at each follow up were tested using the Kruskal-Wallis 1-way ANOVA test for non-normally distributed data.

All statistical analyses were two-tailed. A p value < 0.05 was considered statistically significant for all analyses. Clinically meaningful differences in fatigue were examined in reference to previously applied minimum clinically important difference (MCID) estimates(20-22). The MCID for fatigue was >10 units on the 0-100 SF-36 Vitality subscale.

Latent trajectories of fatigue change were identified using group-based trajectory modelling (GBTM). GBTM is used to cluster individuals who show similar progressions of scores over time and can inform between-group comparisons of differences in outcome. We therefore applied GBTM to determine whether clusters of participants followed similar fatigue trajectories during follow-up.

Specifically, GBTM for censored normal data was used, as the SF-36 VT is a continuous scale, with a minimum value of 0 (maximum fatigue) and a maximum value of 100 (minimum fatigue). Initially, the existence of four plausible cubic trajectories was proposed. Trajectories were then added or removed in consultation with the model-fit statistics, and clinical interpretation of the model, until the best-fitting model was identified. The best-fitting number of trajectories is determined as the model with the lowest Bayesian Information Criterion (BIC), provided there is sufficient support for the complexity of a model. A model with additional trajectories was accepted if the log Bayes factor was greater than six ($2\log_e(B_{10} \geq 6)$). Model fit was then further improved by specification of the correct order polynomial (e.g. liner, cubic, quadratic) for each trajectory.

Characteristics of each GBTM group were defined using the data collected. Differences in fatigue scores at each follow up within the GBTM group and differences between the GBTM groups were analysed using Freidman's test for repeated measures. Time to remission was analysed using Kaplan-Meier survival analysis and log rank test. Differences in categorical data were analysed using Pearson χ^2 test. Correlations were assessed using Pearson's correlation. Analysis of correlations between fatigue and disease severity, inflammation and creatinine were pre-specified before data collection.

The GBTM analysis was conducted using Stata 14.0 (College Station, TX), all other analyses were performed using SPSS Statistics Version 22 (IBM, Armonk, USA).

Results

Patient characteristics

One hundred and fifty patients with newly diagnosed AAV, of whom 117 of 140 patients were from the MYCYC trial and 33 of 44 patients were from the RITUXVAS trial, and 470 general population controls were included in the study. Controls were older than patients but there was no difference in

the sex ratio (table 1). Patients had high levels of disease activity at baseline. There were no differences in the two trials when comparing the patients' ages, diagnoses, disease activity scores at entry, CRP concentrations, or fatigue scores. Due to protocol differences related to the inclusion criteria, patients recruited to the RITUXVAS trial had worse renal function than those recruited to MYCYC trial (Creatinine RITUXVAS 310μmol (114-443) vs MYCYC 109μmol/l (75-177); p<0.001).

Fatigue change

Patients reported substantial levels of fatigue at diagnosis, which were worse than controls (table 1). The median fatigue score for patients was four times greater than the MCID [18-20] compared to controls (median 30 (IQR 10-48) vs 70 (IQR 55-80).

The median fatigue level improved over the first 6 months with treatment (figure 1) but then remained stable with no differences between fatigue scores at 6, 12 and 18 months. One hundred and five patients (70%) reported a clinically significant improvement in fatigue between baseline and 6 months following the start of treatment. The median change of improvers was 45 (IQR 30-60), 4.5 times the MCID. However, despite improvement from baseline, the median fatigue score for the patient population remained worse at all time points compared with healthy controls (Figure 1). Despite the median change analysis suggesting improvement in fatigue scores this concealed important differences in the longitudinal pattern of fatigue; 25% of patients had deterioration, and 12% of patients had no change in fatigue scores at 6 months compared to baseline. Reductions in fatigue did not correlate with reductions in CRP (r=-0.01; p=0.93), change in disease activity (r=0.13; p=0.17) or change in creatinine (r=0.01; p=0.65) or treatment allocation (p=0.68).

Trajectory analysis

One hundred and ten patients completed all four SF-36 questionnaires and 14 completed only 2 SF36 questionnaires; 12 lacked 6 month data, 23 lacked 12 month data and 25 lacked 18 month data. GBTM identified four distinct groups of patients based on changes (or stability) of their fatigue scores during follow up (BIC all data points: -2369.1, BIC per participant: -2356.3) (figure 2). Model fit was further improved by refining the specification of the order polynomial for each trajectory (BIC all data points: -2348.3, BIC per participant: -2340.7). The four groups identified were:

- Stable low fatigue – patients with low fatigue at trial entry who remained non-fatigued
- Stable high fatigue – patients with high fatigue at trial entry who remained fatigued
- High baseline fatigue improvers – patients with high fatigue at trial entry who improved over time
- Moderate baseline fatigue improvers – patients with moderate fatigue at trial entry who improved over time

The fatigue scores over time were compared within each GBTM group (table 2). The Stable low fatigue group (15%), reported median fatigue scores which were comparable to controls at baseline (stable low fatigue group median 70 (IQR 60-75) controls median 70 (IQR 55-80); p=0.77) and did not change over 18 months. In contrast, the Stable high fatigue group reported high median levels of fatigue at baseline median 30 (15-45) which did not improve over time. The Stable high fatigue group were more fatigued than the three other patient groups and controls at 18 months (Stable high fatigue median 30 (IQR 15-40), High baseline fatigue improvers median 55 (IQR 45-70), Moderate baseline fatigue improvers median 80 (IQR 70-85), Stable low fatigue median 65 (IQR 50-70), controls median 70 (IQR 55-80); p<0.001). In the six months following treatment initiation, the Moderate baseline fatigue improver group achieved a median reduction in fatigue of four times the MCID (baseline median 40 (IQR 30-49) vs 6 months median 80 (IQR 70-80)). The High baseline fatigue improver group achieved a less rapid, but continued fatigue improvement until month 12

(Table 2). However, at 18 months this group continued to have worse fatigue levels than controls (median 55 (IQR 45-70) vs median 70 (IQR 55-80); p<0.001).

Group characterisation sought to identify robust baseline markers which differentiated those who would remain fatigued (Stable high fatigue) from those who improved over time. This would allow early identification of those most in need of fatigue-specific interventions. Therefore, patients in the Stable high fatigue group were compared with the two groups of patients whose fatigue improved. Stable low fatigue patients were excluded as their fatigue levels were not different from controls at baseline. There were no differences in demographics variables between the three groups compared. Disease activity was lower in the Stable high fatigue group compared to the two groups whose fatigue improved (table 3). Additionally, there were no differences in the other SF-36 domains at baseline which differentiated the Stable high fatigue patients from the patients who improved (data not shown).

Stable high fatigue patients had lower BVAS scores at diagnosis compared to improvers. As there were no other demographic differences at diagnosis, we investigated whether there was any difference in time to remission or disease relapse over the first six months, as this was the period of fatigue improvement. Seven patients failed to achieve remission in the three fatigued groups; there were no differences in the time to remission (log rank=2; p=0.57) or relapse rates during follow up (table 3). At six months there were no differences between the three trajectory groups in renal function, damage (VDI) or inflammation levels (CRP).

Discussion

In this cohort of patients with incident AAV recruited to two clinical trials fatigue levels were worse than a control population. The extent and nature of the fatigue experienced by the patients in this

study is comparable with that reported in our previous studies(6) and in other rheumatological diseases. We have shown that, on average, fatigue responds well to treatment amongst AAV patients. However, using GBTM we identified important differences in an individual's symptom change and identified a group of patients whose fatigue did not improve. In doing so, this study assessed the longitudinal response of fatigue in patients with AAV using trajectory analysis. We propose that such analytic approaches are crucial for patient-reported outcomes such as fatigue, which are subjective and have a multi-factorial aetiology. This study provides patient level detail of the course of fatigue in AAV and information on the prognosis of fatigue, sorely needed by patients, identifying those who may require additional treatment focussed on fatigue rather than disease activity.

Patients in the Stable high fatigue group had lower levels of vasculitis activity at diagnosis (BVASv3 score) compared to those whose fatigue improved over the first six months from diagnosis. Although the differences were statistically significant, there was considerable overlap in disease activity and fatigue between patient groups such that these factors did not predict, at an individual level, whose fatigue would fail to improve. It is unclear why those patients with High stable fatigue had lower disease activity compared to those patients who improved. There were no other disease characteristics that associated with persistent fatigue, specifically no association with renal function or inflammation.

The lack of association with disease characteristics supports the suggestion that the aetiology of fatigue in these patients is multi-factorial and disease associated inflammation plays only a small part. .

For patients in the High and Moderate baseline fatigue improver groups fatigue improved with treatment whereas for the other groups there was no change in fatigue despite treatment and

improvement in disease activity. Reductions in fatigue showed no association with change in C-reactive protein, a surrogate marker of inflammation. Despite no difference in the percentage of patients in remission or disease activity at 6 months the trajectory of fatigue differed between the 4 groups. Our original cross-sectional study showed only a small association of fatigue with inflammation. CRP was categorized as raised or normal and those with a raised CRP had a 3.7 odds ratio with wide confidence intervals (95% confidence intervals 1.7, 8.1)(10) and the population attributable risk was only 6%. Further, a recent publication looking at response of fatigue to treatment with anti-TNF medication suggested that most of the improvement was driven by improvements in pain(22). Others have also emphasized the importance of sleep in modifying fatigue and central pain processing(23)

We and others have shown that patient-reported domains such as pain, poor sleep and the ability to cope with illness may be more important in the development of fatigue in AAV(10) and other autoimmune conditions such as RA (24) than disease activity(25). Previous work in RA populations suggests that those with a history of depression are more likely to report greater fatigue in the future(26, 27). Our previous work has also suggested correlations between fatigue and anxiety and depression in patients with AAV (9), however this study was cross-sectional. Given the substantial impact of fatigue on both patients and society, the results support the argument that fatigue is a symptom that must be targeted in its own right rather than being improved as part of a secondary benefit to existing interventions.

There are several limitations to this study. The population included 150 patients and small effect sizes may have been missed. However this is a rare disease, it was an incident cohort, and data was collected prospectively. Interestingly, we have found that patients in the High stable fatigue group had lower disease activity than those whose fatigue improved. This has not been shown previously. The data collected was unable to explain this finding. We did not collect co-morbidity data, including

psychological co-morbidity, however, this was a more homogeneous population than other studies as all patients had new onset disease. It is recognised that these patients were recruited to clinical trials from secondary and tertiary care centres where clinicians are experienced in the management of AAV patients, which may affect patient reported outcomes. Despite 25% of our patients reporting a worsening of fatigue scores at six months we could not identify such a group using our trajectory analysis, suggesting the study may have been under-powered and needs repeating in a larger group. In addition, although the SF-36 vitality score is a valid tool for measuring fatigue(18, 19) and has good psychometric properties(28), it may under-perform at higher levels of fatigue compared to other tools in some chronic diseases(29). Identification of those patients with a worse fatigue trajectory may require use of more sensitive fatigue measures. Our study had a short follow up of only 18 months and it is unclear what happens to fatigue levels beyond this timeframe. However, we did note that fatigue levels in the patients who improved did not change between 12 and 18 months. Questionnaires were administered at 6 monthly intervals, which may have missed transitory changes in fatigue levels. However, we were interested in persistent chronic fatigue; the SF-36 Vitality domain has a recall of one month.

In summary, the data suggest that fatigue is common in patients with AAV but average changes in fatigue are poorly informative of the variability in patterns of changes in fatigue over time. The majority of patients presenting with AAV will experience fatigue which will improve but may not return to normal levels. In addition there is an important sub-group with high levels of fatigue at baseline who show no improvement in fatigue levels. These patients have lower levels of vasculitis activity at diagnosis. Further investigation of baseline differences in larger populations is required to understand this finding. Patients with persistent fatigue may be more likely to benefit from non-pharmaceutical interventions addressing biopsychosocial symptoms such as pain, and social function strategies, which could be commenced at six months when patients are in remission. Further evaluation of such interventions is essential in order to address the unmet need of treatment for this important problem.

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Disclosures – LH, DJ, RB. have received research grants and speakers fees from J Hofman La Roche. LH, RB, DJ, MM have been involved in studies in which rituximab was given free of charge by Roche and Mycophenolate was given free of charge by Vifor (previously Aspreva).

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Figure Legends

Figure 1 Data presented as boxplots noting median, IQR and outliers of fatigue scores at each time point for all patients and healthy controls. The fatigue score is reverse scored with 0 indicating maximum fatigue and 100 indicating minimum fatigue.

[0] $p<0.001$ fatigue score at time 0 compared with 6 months.

** $p<0.001$ time point compared with control

Figure 2

Trajectory analysis identified 4 distinct groups of patients based on changes (or stability) of their fatigue

Tables

Table 1 Patient Characteristics at baseline

	controls n=470	Patients n=150	Significance
Age (years)	61.5 ± 13.6	57.9±17.5	p=0.002
Sex (m/f)	223/247	76/74	p=0.512
Trial (MYCYC/RITUXIVAS)		117/33	
Diagnosis (MPA/GPA)		58/92	
ANCA (MPO/PR3/negative/unknown)		54/90/3/2	
VDI at diagnosis		0 (0-0)	
Disease activity (BVASv3 score) at diagnosis		19 (13-24)	
Creatinine at diagnosis (μmol/L)		124 (80-231)	
C-reactive protein (mg/L)		22 (7-72)	
Fatigue	70 (55-80)	30 (10-48)	p<0.001

Abbreviations: n, number; m, male; f, female; MYCYC, mycophenolate versus cyclophosphamide for induction therapy; RITUXVAS, rituximab versus cyclophosphamide for induction trial; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; ANCA, anti-neutrophil cytoplasm antibody; MPO, myeloperoxidase; PR3, proteinase 3; VDI, vasculitis damage index; BVASv3, Birmingham vasculitis activity score version 2003. Median and IQR are shown apart from age (mean ± SD).

Table 2 Fatigue score of each GBTM group associated with time

	Stable high fatigue n=37	High baseline fatigue improvers n=61	Moderate baseline fatigue improvers n=29	Stable low fatigue n=23	Controls
time 0	30 (15-45)	15 (5-25)	40 (30-49)	70 (60-75)	70 (55-80)
time 6 months	25 (15-40)	45 (40-55)	80 (70-80)	60 (50-65)	
time 12 months	28 (20-40)	58 (50-66)	80 (75-90)	70 (50-80)	
time 18 months	30 (15-40)	55 (45-70)	80 (70-85)	65 (50-70)	
p value	p=0.81	p<0.001	P<0.001	p=0.11	

Fatigue score of each GBTM group associated with time. P values are derived from Friedman's test for repeated measures for change in fatigue score over time within the GBTM group.

Abbreviations: n, number; GBTM, group-based trajectory modelling. Data presented as median and IQR.

Table 3 Group Characteristics

Group	Stable high fatigue	High baseline fatigue improvers	Moderate baseline fatigue improvers	stable low fatigue	P value
n=	37	61	29	23	
sex M/F (M%)	18/19 (49%)	31/30 (51%)	14/15 (48%)	13/10 (56%)	0.966
diagnosis GPA/MPA (%GPA)	20/17 (54%)	43/18 (70%)	16/12 (55%)	13/10 (56%)	0.179
trial MYCYC/RITUXVAS (%MYCYC)	28/9 (75%)	50/11 (81%)	22/6 (76%)	17/6 (74%)	0.69
Treatment (MMF/CYC/Rit)	14/18/5	27/25/9	7/16/6	10/9/4	0.46
Age (years)	62.0±18	55.3±17	55.8±18	61.8±15	0.201
BVAS at entry	14 (12-21)	21 (15-25)	20 (14-25)	18 (12-21)	0.014
BVAS at 6 months	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.15

VDI at 6 months	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	0.56
CRP at baseline (mg/L)	16 (4-88)	22 (8-61)	28 (8-90)	28 (6-78)	0.977
CRP at 6 months (mg/L)	3 (1-7)	3.5 (1-7.6)	2.7 (1-4.2)	5 (2-18)	0.162
Creat at baseline (µmol/l)	115 (67-353)	119 (83-209)	150 (92-209)	116 (78-223)	0.889
Creat at 6 months (µmol/l)	105 (70-205)	98 (78-116)	106 (95-126)	105 (87-185)	0.451
Patients achieving remission (%)	35 (95%)	56 (92%)	27 (93%)	22 (96%)	0.708
Patients who relapsed (%)	15 (41%)	15 (25%)	6 (21%)	5 (22%)	0.213

Abbreviations: n, number; M, male; F, female; MYCYC, mycophenolate versus cyclophosphamide for induction therapy; RITUXVAS, rituximab versus cyclophosphamide for induction trial; CYC, cyclophosphamide; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; GPA,

granulomatosis with polyangiitis; BVAS, Birmingham vasculitis activity score version 2003. Median and IQR are shown apart from age (mean ± SD).

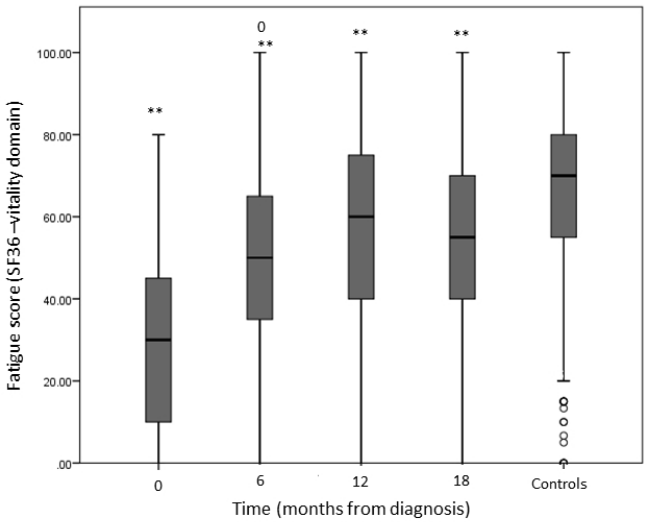

Figure 1

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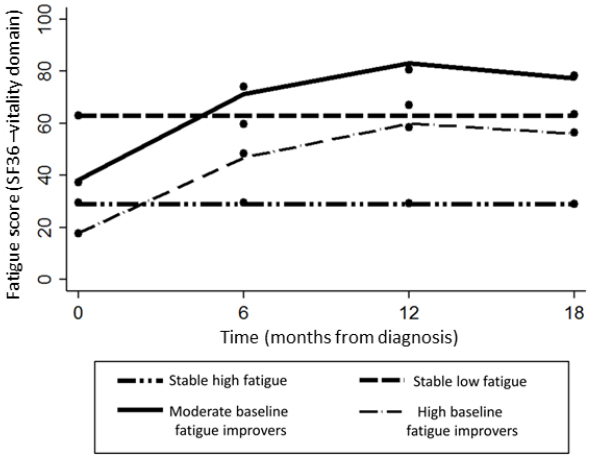

Figure 2

254x190mm (96 x 96 DPI)